REMARKS

Claims 1-22 were pending. Claims 1-9 and 17-22 were withdrawn by the Examiner. Claims 11-12 were canceled. Claims 10, 13, 14 and 16 were amended. Claim 10 was amended to incorporate the limitations of claim 1, to limit the claim to a process for preparing a chemical conjugate between an immunoglobulin Fab fragment and molecular entities imparting diagnostic utility, and to specify that the selective and quantitative reduction of inter-chain disulfide bond of the Fab fragment occurs with TCEP at concentrations ranging from 0.1 to 10mM. Claim 13 was amended to correct the dependency and to remove the superfluous phosphine concentration limitation. Claims 14 and 16 were amended to require a TCEP concentration of 0.5 – 5 mM.

Priority

Applicants thank the Examiner for acknowledging the priority claim under 35 U.S.C. 119.

Information Disclosure Statements

Applicants thank the Examiner for considering the references in the Information Disclosure Statements identified as being filed on April 22, 2005 and October 15, 2005. Applicants respectfully note that the second of the two Information Disclosure Statements was actually filed on *October 12, 2007*. Applicants are submitting herewith an IDS including copies of the references missing from the January 16, 2007 Information Disclosure Statement and ask that the examiner consider these references.

Drawings

The Examiner objects to the drawings as allegedly failing to show the migration described in the specification. Applicants respectfully traverse. As an initial matter, Applicants

understand this objection to be directed to Figure 3, the only figure showing changes in migration distances. Figure 3 is described at page 18 as cited by the Examiner and explained in detail on page 24 in Example 5. As explained in Example 5, in Figure 3 native electrophoresis was used to show the differences in charge introduced by the DTPA derivative after conjugation with Compound D. In each case the Fab preparations conjugated with Compound D (lanes 2, 4 and 6) showed the same reduction in migration distance towards the cathode when compared with the corresponding unconjugated Fab preparation (lanes 1, 3 and 5 respectively). The reduction in migration distance that follows conjugation with Compound D confirms the attachment of a definite number of negatively charged groups and thus the controlled stoichiometry of the claimed method. Looking at Figure 3 the shortened migration distance in lanes 2, 4 and 6 is apparent in comparison to lanes 1, 3 and 5; thus Applicants submit that Figure 3 includes all structural details essential for a proper understanding of the invention and is in full compliance with37 C.F.R 1.83(a).

Rejections Under 35 U.S.C. § 112

The Examiner rejected claims 11 and 13-16 for alleged indefiniteness for including a broad range together with a narrow range in the same claim. Applicants submit that the cancellation of claim 11 and the amendment of claims 13-16 render this rejection moot.

Rejections Under 35 U.S.C. § 102

Claim 10 was rejected under 35 U.S.C. 102 for alleged anticipation by Hansen et al WO 91/04056 ("Hansen"). Applicants respectfully traverse. Claim 10 requires that the selective and quantitative reduction of inter-chain disulfide bond of the Fab fragment occurs with TCEP at concentrations ranging from 0.1 to 10mM. Hansen does not disclose use of TCEP to

reduce inter-chain disulfide bonds, but rather, as the examiner concedes, discloses the use of cysteine to reduce the Fab fragment; thus it cannot anticipate claim 10 for at least this reason.

Claims 10-13 and 15 were rejected under 35 U.S.C. 102 for alleged anticipation by Maurer et al WO 02/056907 ("Maurer"). Applicants respectfully traverse. Claims 10-13 and 15 require a chemical conjugate between a Fab fragment and molecular entities imparting diagnostic utility, wherein the selective and quantitative reduction of inter-chain disulfide bond of the Fab fragment occurs with TCEP at concentrations ranging from 0.1 to 10mM and wherein the stoichiometric molar ratio of molecular entity to Fab fragment in the conjugates is in the range from 0.95 to 1.05 or in the range from 1.95 to 2.05. Maurer teaches a method of coupling a Fab fragments to Qβ capsid protein, a protein useful for vaccination, but not diagnostically useful. Furthermore, Applicants note that contrary to the Examiner's assertion, Maurer does not teach or suggest use of TCEP in a concentration of 0-1000mM. Rather, Example 16 of Maurer states that varying concentrations of TCEP or DTT were used, ranging from "0-1000 μM" , Moreover, as explained in detail below, Maurer fails to teach a method in which stoichiometry can be controlled to meet the claimed stoichiometric ratios.

In summary, neither Hansen nor Maurer teach all of the limitations of claims 10-13 and 15; thus these claims are not anticipated.

Rejections Under 35 U.S.C. § 103

Claims 14 and 16 were rejected under 35 U.S.C. for alleged obviousness over Maurer as evidenced by Cruse and Lewis, Illustrated Dictionary of Immunology, Boca Raton, FL 1995 ("Cruse and Lewis"). The examiner asserts that Maurer teaches a method of coupling Fab fragments to Qβ capsid proteins using, inter alia, concentrations of DTT or TCEP ranging from "0-1000mM". While conceding that Maurer does not explicitly teach that the Fab concentration

is from 1.5-10 μM or 1-5 μM or that the conjugate concentration is 0.1-100mM, the Examiner asserts that it would have been obvious to optimize the concentration of the Fab fragment and the resulting conjugate moiety. Applicants respectfully traverse.

"The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385, 1396 (2207) noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit." MPEP Section 2143.

"The rationale to support a conclusion that the claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art." 83 UDPQ2d at 1395 and MPEP Section 2143. Further, a prima facie case of obviousness based on structural similarity is rebuttable by proof that the claimed compounds possess unexpectedly advantageous or superior properties. (MPEP 2144.09).

Applicants respectfully assert that the combination of the cited references does not teach or suggest all of the claim limitations and that the claimed compounds possess unexpectedly superior properties. Therefore, applicants respectfully traverse the § 103 rejection.

The claimed invention is directed to a process for preparing diagnostic agents and, more particularly, it relates to a process for preparing a chemical conjugate between an immunoglobulin Fab fragment and a diagnostic moiety. As explained supra, Maurer, incontrast is directed to producing conjugates for vaccines and neither teaches nor suggests diagnostic conjugates. Additionally, unlike Maurer, the present process provides for a diagnostic entity with a controlled stoichiometry of conjugation (e.g. the stoichiometric molar ratio of molecular

entity to Fab fragment in the conjuagates is in the range from 0.95 to 1.05 or in the range from 1.95 to 2.05).

Being able to control the stoichiometric ratio during conjugation is of the utmost importance as it allows for chemically defined conjugated diagnostic compounds, in comparison to the rather complex and poorly defined mixtures of conjugated compounds obtained according to the process of Maurer, wherein each of the conjugates in the obtained mixture may have its own stoichiometry of substitution and thus, the claimed stoichiometric ratios cannot be achieved.

Indeed, Example 16 of Maurer establishes that each of the successful couplings between the Fab fragment and the protein (see lanes 5-8 and lanes 10-12 of figure 21) is part of a very complex mixture in which only a portion includes the desired conjugate (with average MW of 40 kDa, shown by an arrow in figure 21). Due to the inability of the Maurer method to control stoichiometry, extensive, expensive and impractical separation methods must be used to isolate the derivative of interest from the complex mixture containing it.

In contrast, in the present invention, the claimed method unexpectedly yields controlled stoichiometry of substitution through the selective and quantitative reduction of the inter-chain disulfide bond of a Fab fragment using TCEP at concentrations ranging from 0.1 to mM so as to provide for two sulfhydryl groups to be then reacted with the diagnostic moiety or moieties bearing free sulfhydryl reactive groups. Neither the method nor the advantages are taught or suggested by Maurer.

The secondary reference, Cruse and Lewis, fails to remedy the deficiencies of Maurer. Indeed, it was cited by the Examiner for the molecular weight of the Fab of Maurer and fails to teach or suggest the claimed methods. Whether taken alone or together, the cited references fail to teach or suggest the claimed methods, which provide diagnostic conjugates of

controlled stiochiometry and specified stoichiometric ratio through the selective and quantitative reduction of the inter-chain disulfide bond of a Fab fragment using TCEP at concentrations ranging from 0.1 to 10 mM.

In view of the present amendments and foregoing remarks, reconsideration of the rejections and advancement of the case to issue are respectfully requested.

No fee is believed to be necessary in connection with the filing of this Amendment and Response to Restriction Requirement. However, if any additional fee is necessary, applicant hereby authorizes such fee to be charged to Deposit Account No. 50-2168.

Respectfully submitted,

Dated: July 2, 2008

M. Caragh Noone, Reg. No. 37,197
Bracco Research USA Inc.
305 College Road East
Princeton, NJ 08540
Tel: (609) 514-2454
Fax: (609) 514-2446